REMARKS

In view of the above amendments and the following remarks, the Examiner is respectfully requested to withdraw the rejections and allow Claims 16-17, 19-32 and 51-66, the only claims pending and under examination at this time.

Claims 16, 23, 32, 51, 57 and 62 have been amended as suggested by the Examiner. As the above amendments add no new matter, their entry by the Examiner is respectfully requested.

Turning now to the rejections presented in the Office Action, Claims 16, 17, 19-32 and 51-66 were rejected under 35 U.S.C. § 112, 2nd ¶. In view of the above amendments that adopt the Examiner's suggestion for overcoming this rejection, it is respectfully submitted that this rejection may be withdrawn.

Finally, Claims 16, 17, 19-32 and 51-66 were rejected under 35 U.S.C. 103(a) as being obvious over Nygren and Pouletty. In making this rejection, the Examiner avers that because Nygren teaches a "bifunctional" molecule of a polypeptide active agent bonded to a polypeptide serum protein targeting agent, and Pouletty teaches a bifunctional molecule that includes a binding moiety for a drug, it would be obvious to modify these previously disclosed "bifunctional" molecules to include a small molecule drug.

Nygren actually discloses large fusion proteins of a first protein domain that exhibits a desirable activity (e.g., tPA, hGH, IFG-I, IFG-II, TNF, EFG, insulin, relaxin) and a second serum protein targeting domain (e.g., an albumin binding domain). These fusion proteins are much larger that 5000 daltons. As such, the "bifunctional" molecules diclosed by Nygren greatly exceed the size limitation of the bifunctional molecules employed in the claimed methods of the present application. As further developed

below, Nygren therefor fails to teach or suggest the claimed methods because Nygren fails to teach or suggest the bifunctional molecules employed in the claimed methods.

With respect to Pouletty, Pouletty's disclosure is completely different from the claimed methods. Pouletty's bifunctional molecules do not include a drug moiety as claimed because a free "drug" is the target of Pouletty's bifunctional molecule, there is no drug moiety or free drug component that is part of Pouletty's bifunctional molecule. Specifically, Pouletty's bifunctional molecules are made up of first and second binding members. The first binding member is specific to or binds with a "detrimental blood borne agent (which the Examiner apparently equates with a drug). The second binding memberis specific for a so-called "anchor" protein (which the Examiner apparently equates with a presenter protein). As such, Pouletty's bifunctional molecule does not include the claimed drug moiety, but instead provides a moiety that targets and binds to a harmful "drug" (a detrimental blood borne agent).

In contrast, the bifunctional molecules employed in the presently claimed methods have the formula:

ZX

where X is a drug moiety and Z is a ligand for a presenter protein (Z and X may be separated by a linker L). The X moiety of the bifunctional molecules employed in the claimed methods is a drug; it is not something that *binds to* a detrimental blood borne agent as in Pouletty. Nor is X a free drug, as is the detrimental blood borne agent in Pouletty, waiting to interact with a specific target in the host. As claimed, it is instead a part of the bifunctional molecule.

As such, Pouletty's bifunctional molecules are clearly structurally different from the bifunctional molecules employed in the claimed methods. This structural difference manifests itself in a completely different mode of action. Where Pouletty uses a bifunctional molecule to trap, anchor and remove a free detrimental blood borne agent, the claimed method attaches a drug to a presenter protein in order to enhance the pharmacokinetic properties of th drug.

Furthermore, analogous to Nygren, Pouletty also discloses large bifunctional molecules. Specifically, Pouletty discloses bifunctional molecules that are conjugates of two different antibodies or specific binding fragments thereof, i.e., a first antibody that specifically binds to a blood borne agent, e.g., a drug of abuse, and a second antibody that specifically binds to long lived blood protein, e.g., serum albumin.

As such, both Nygren and Pouletty teach "bifunctional" molecules that have molecular weights far in excess of 5000 daltons. Furthermore, since Nygren is concerned with large fusion proteins of a pharmaceutically active protein and Pouletty is concerned with large bifunctional molecules of two different antibodies or fragments thereof, these teachings fail to even suggest a small bifunctional molecule that does not exceed about 5000 daltons.

In contrast, the claimed methods are limited such that the bifunctional molecule administered in the claimed methods is one that does not exceed about 5000 daltons. As such, the claimed methods are limited to ones in which a bifunctional molecule much smaller than those taught or suggested by Nygren or Pouletty is employed. Accordingly, for at least this reason, the claimed methods are not obvious over the combined teachings of Nygren and Pouletty.

Furthermore, with respect to Claims 19, 24, 29, 53, 58 and 63, these claims are all limited to the embodiment where the modulating moiety binds to an intracellular protein. As characterized by the Examiner, both Nygren and Pouletty are limited to bifunctional compounds that bind to extracellular proteins, e.g., serum albumin. Neither Nygren nor Pouletty teach or suggest a bifunctional molecule that includes a modulating moiety which binds to an intracellular moiety.

Accordingly, Claims 16, 17, 19-32 and 51-66 are not obvious under 35 U.S.C. 103(a) over Nygren and Pouletty and this rejection may be withdrawn.

CONCLUSION

In view of the above amendments and remarks, this application is considered to be in good and proper form for allowance and the Examiner is respectfully requested to pass this application to issuance.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815.

Respectfully submitted,

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Date: 7.24.03

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